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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/680,076	10/06/2003	Thomas Bell	36-02	9942

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EXAMINER	
COLEMAN, BRENDA LIBBY	
ART UNIT	**PAPER NUMBER**
1624	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/680,076	BELL ET AL.	
	Examiner	Art Unit	
	Brenda L. Coleman	1624	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *30 March 2007*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *29-63* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *29-63* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *3/30/07*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Claims 29-63 are pending in the application.

This action is in response to applicants' amendment dated March 30, 2007. Claims 29, 30 and 60 have been amended, claims 14 and 24 have been canceled and claims 61-63 are newly added.

Response to Arguments

Applicant's arguments filed March 30, 2007 have been fully considered with the following effect:

1. With regards to the 35 U.S.C. § 112, first paragraph rejection of claims 29-38, 40-42 and 58-60 in the previous office action, the applicants' arguments have been considered but are not found persuasive. The applicants' stated, that "the specification need not disclose what is well known in the art" and that § 112 requires that, "unless the information is well known in the art, the application itself must contain this information". The expression triaza mazcrocyclic in conjunction with the definitions of a, b, c, d, e and W forms a 6 to 46 atom rings containing 3 nitrogen atoms includes an extensive number of rings of which are neither supported or contemplated by means of a sufficient disclosure and/or examples. The Ring Index, which lists ring systems used in organic chemistry provided by the American Chemical Society defines various rings which would fit under the applicants' Markush group, such as 1,3,5-triazine, 1,3,5-triazepine, 1,3,5-triazocine, 1,3,6-triazocine, 1,3,7-triazecine, etc. The nature of the invention in the instant case has claims, which embraces substituted 1,5,9-triazadodecane compounds.

The applicants' also state, that "presumably the '161 issued US patent provides

an enabling disclosure of how to make the various triaza compounds whose uses are claimed therein". First, I will not comment on that which was done by others in other applications and/or patents. I am not aware of the facts in those applications and hence am not in a position to comment on what was done by another examiner. I can only comment on the facts of the instant application as set forth above.

Claims 29-38, 40-42 and 58-63 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention, for reasons of record and stated above.

2. With regards to the 35 U.S.C. § 112, first paragraph rejection of claims 29-60 in the previous office action, the applicants' arguments have been considered but are not found persuasive. The applicants' state that the CD4 down-regulation assays are screening protocols for identifying compounds which are useful for treatment of autoimmune disorders and inflammation which are ameliorated by suppression of CD4+-T-cell-mediated immune response and the applicants further submit that the results of CD4 expression assays are evidence that the compounds tested are useful in the therapeutic methods as claimed. However, recent journal article, of Fehervari et al., herein provided indicates that a large body of data from murine studies have demonstrated the potent ability of both natural and adaptive regulatory $CD4^+$ T cells to control immune responses under a wide range of clinically important conditions. Fehervari is speculative at best to the clinical applications of $CD25^+$ $CD4^+$ T_R cells.

Fehervari further lists the major hurdles to the development of regulatory T cells as an immunotherapy such as identification of unambiguous surface markers for the isolation of human T_R cells; clear delineation of the molecular mechanism of T_R cell mediated suppression; characterization of the signals both downstream and upstream of *Foxp3*; identification of factors capable of viably expanding T_R cells *ex vivo*; and resolving the accuracy to which *FOXP3* can be used as a marker in human cells.

As stated in the MPEP, 2164.08 "[t]he Federal Circuit has repeatedly held that the specification must teach those skilled in the art how to make and use the full scope of the claimed invention without undue experimentation. In re Wright, 999 F.2d 1557, 1561 27 USPQZd 1510, 1513 (Fed. Cir. 1993). Nevertheless, not everything necessary to practice the invention need be disclosed. In fact, what is well-known is best omitted. In re Buchner, 929 F.2d 660, 661, 18 USPQZd 1331, 1332 (Fed. Cir. 1991). All that is necessary is that one skilled in the art be able to practice the claimed invention, given the level of knowledge and skill in the art. Further the scope of enablement must only bear a reasonable correlation to the scope of the claims. See, e.g., In re Fisher, 427 F.2d 833, 839,166 USPQ 18, 24 (CCPA 1970). As concerns the breadth of a claim relevant to enablement, the only relevant concern should be whether the scope of enablement provided to one skilled in the art by the disclosure is commensurate with the scope of protection sought by the claims. In re Moore, 439 F.2d 1232, 1236, 169 USPQ 236, 239 (CCPA 1971). See also Plant Genetic Sys., N.V. v. DeKalb Genetics Corp., 315 F.3d 1335, 1339, 65 USPQZd 1452, 1455 (Fed. Cir. 2003) (alleged pioneer status of invention irrelevant to enablement determination."

Claims 29-63 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention, for reasons of record and stated above.

3. The applicants' amendments are sufficient to overcome the 35 U.S.C. § 112, first paragraph rejection labeled paragraph 6) of the last office action, which is hereby **withdrawn**.

4. The applicants' amendments are sufficient to overcome the 35 U.S.C. § 112, second paragraph rejections labeled paragraph 7b), c), d), e) and g) of the last office action, which are hereby **withdrawn**. However, with regards to the 35 U.S.C. § 112, second paragraph rejection labeled 7a), f) and h) in the last office action, the applicant's amendments and remarks have been fully considered but they are not persuasive.

a) The applicants' stated that the term "charged group" is understood in the art, particularly in view of the examples of charged groups, which are given in the specification e.g., on page 4, line 1 and that with respect to the counter-ions, the claim is directed to the use of compounds of the listed formula and pharmaceutically acceptable salts thereof. One of ordinary skill in the art understands that pharmaceutically acceptable salts include appropriate pharmaceutically acceptable counter-ions. However, the claims are to the method for treating ..... comprises the step of administering to the individual a

therapeutically effective amount or combined amount of one or more triaza macrocyclic **compounds**, and compounds are not ions.

Claims 29, 31-39, 41, 42 and 58-63 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention, for reasons of record and stated above.

f) The applicants' stated that an inadvertent error is corrected in claim 46 by replacing "-SO_2" with "-SO_2-". However, Claim 46 has not been amended.

Claim 46 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention, for reasons of record and stated above.

h) The applicants' stated that this recitation indicates that it is appreciated and understood in the art that, CD4+ T-cells contribute to inflammatory responses and autoimmune diseases, including those listed. Applicants have demonstrated that the triaza compounds as claimed function to down-regulate CD4 expression in T cells (see Example 1 and Table 1). Applicants have further demonstrated that this down regulation is specific for CD4 compared to a variety of surface antigens (Table 2). Thus, in view of the data presented in the specification and in view of the understanding in the art that CD4+ T-cells contribute to inflammatory responses and autoimmune diseases, one of ordinary skill in the art would understand and appreciate that compounds of this invention

are useful in the treatment of inflammatory and autoimmune diseases. However, as point out above in response to the applicants first paragraph rejection Fehervari is speculative at best to the clinical applications of $CD25^+$ $CD4^+$ T_R cells. Fehervari further lists the major hurdles to the development of regulatory T cells as an immunotherapy such as identification of unambiguous surface markers for the isolation of human T_R cells; clear delineation of the molecular mechanism of T_R cell mediated suppression; characterization of the signals both downstream and upstream of *Foxp3*; identification of factors capable of viably expanding T_R cells *ex vivo*; and resolving the accuracy to which *FOXP3* can be used as a marker in human cells. Hence it is not known what is meant by treating an individual suffering from a pathological conditions which is ameliorated by suppression of CD4+-T-cell-mediated immune response, i.e. the scope of the claims must be clear so that the public is informed of the boundaries of what constitutes infringement of the patent. The rejection of claims 29-63 was on the grounds that it is indefinite, in that it is not known which diseases are capable of being responsive to the suppression of CD4+-T-cell. The scope of diseases and/or disorders associated with the suppression of CD4+-T-cell could alter over time. Thus the applicants' are not entitled to preempt the efforts of others.

Claims 29-63 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject

matter which applicant regards as the invention, for reasons of record and stated above.

5. The applicants' amendments are sufficient to overcome the 35 U.S.C. § 102, anticipation rejection labeled paragraph 8) of the last office action, which is hereby **withdrawn**.

In view of the amendment dated March 30, 2007, the following new grounds of rejection apply:

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

6. Claims 29-32, 35-40, 43-47, 51-55 and 58-63 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter, which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. The amendment to the definition of the substituents of Ar, which was amended to include the moieties one or more acyl groups and one or more acid or ester groups is not described in the specification with respect to the genus.

Applicant is required to cancel the new matter in the reply to this Office action.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter, which the applicant regards as his invention.

7. Claims 29-63 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. The following reason(s) apply:

a) Claim 29 and claims dependent thereon are vague and indefinite in that it is not known what is meant by an alkenyl having one carbon atom in the definition of the R' within the definition of the polar substituents.

b) Claim 29 and claims dependent thereon are vague and indefinite in that it is not known what is meant by an alkenyl having one carbon atom in the definition of the R' within the definition of the non-polar substituents.

c) Claim 29 and claims dependent thereon are vague and indefinite in that it is not known what is meant by alky in the definition of R_{Ar}. It is believed that the applicants' intended alkyl.

d) Claim 29 and claims dependent thereon are vague and indefinite in that it is not known what is meant by C_e where C_e represents a carbon bridge between the nitrogens. There is no C_e in the formula.

e) Claim 29 and claims dependent thereon are vague and indefinite in that it is not known what is meant by the definition of e in the second from the last line in the claim. The subscript e is on W and not a C.

Conclusion

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Brenda L. Coleman whose telephone number is 571-272-0665. The examiner can normally be reached on 9:30-6:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, James O. Wilson can be reached on 571-272-0661. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR.

Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Brenda Coleman

Brenda L. Coleman
Primary Examiner Art Unit 1624
Friday, June 08, 2007